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Joana Vicente Vargas

Evaluation of Central Nervous System involvement in SLE patients. Screening psychiatric manifestations – A Systematic Review

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Evaluation of Central Nervous System involvement in SLE patients. Screening psychiatric manifestations – A Systematic Review

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Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

Nome: Joana Vicente Vargas

Endereço eletrónico: joanavvargas@gmail.com **Telefone ou Telemóvel**: 918778831

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Avaliação do envolvimento do Sistema Nervoso Central em doentes lúpicos.

Rastreio de manifestações psiquiátricas – Revisão Sistemática

Joana Vicente Vargas
Aluna do 6º ano do curso de Mestrado Integrado de Medicina
da Faculdade de Medicina da Universidade do Porto

Serviço de Reumatologia do Hospital de São João
Faculdade de Medicina da Universidade do Porto

Alameda Prof. Hernâni Monteiro
4200-319 Porto, Portugal

med06038@med.up.pt

Evaluation of Central Nervous System involvement in SLE patients. Screening psychiatric manifestations – A Systematic Review

Avaliação do envolvimento do Sistema Nervoso Central em doentes lúpicos. Rastreio de manifestções psiquiátricas – Revisão Sistemática

Abstract: Cognitive dysfunction, mood and anxiety disorders are three out of the five psychiatric syndroms included in Neuropsychiatric Lupus. These manifestations are among the most prevalent in SLE having an important impact on patients quality of life. However, the unknown etiology allied to the lack of clarity on the best diagnosis procedure, makes early diagnosis dificult. This manuscript reviews the recent literature on the screening intruments focused on identifying lupus patients with probable psychiatric manifestations.

***Resumo**: Disfunção cognitiva, distúrbios do humor e ansiedade são três das cinco síndromes psiquiátricas incluídas na Lupus Neuropsiquiatrica. Estas manifestações estão entre as mais prevalentes na lúpus e têm um impacto importante na qualidade de vida destes doentes. Apesar disto, o deconhecimento etiológico aliado à falta de um processo diagnóstico ideal, fazem com que o seu diagnóstico seja por vezes difícil. Neste trabalho é apresentada uma revisão da literatura recente dos instrumentos de rastreio da idetificação de doentes com lúpus com prováveis manifestações psiquiátricas.*

Key-words: Neuropsychiatric Lupus, Screening, Cognitive Dysfunction, Mood Disorders, Anxiety Disorders.

***Palavras-Chave**: Lupus Neuropsiquiátrica, Rastreio, Disfunção Cognitiva, Distúrbios do Humor, Distúrbios da Ansiedade.*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, autoimmune disease characterized by its multi-systemic involvement and multiple clinical manifestations. It can involve the nervous system on its central or peripheral component.

In an effort to standardize nomenclature and diagnostic methodology, the American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus, published in 1999, the case definitions and diagnostic recommendations on Neuropsychiatric Lupus (NPSLE). Nineteen syndromes were included in NPSLE and for each were suggested not only the diagnostic criteria and testing but also associations and exclusions[1]. The publication was widely accepted and has been used ever since in the study of NPSLE in adult and pediatric populations.

Recent studies report a prevalence of neuropsychiatric manifestations of 27-80% in adults[2-8], and 22-95% in children[9-12]. NPSLE can develop in any time during the course of the disease but there are several studies reporting a tendency to occur early in its course[5,8]. Furthermore, association between neuropsychiatric events and disease activity has been reported in some studies[13, 14] and denied in others[15-19].

Five out of 19 syndromes that included in NPSLE are psychiatric and were considered by the ACR Ad Hoc Committee on NPSLE according to the DSM-IV diagnostic criteria: mood disorders, anxiety disorders, cognitive dysfunction, psychosis and acute confusional state.

The importance of studying psychiatric phenomena in lupus disease lies not only in its high prevalence reported[20] but mainly in what it represent clinically and socioeconomically. Psychiatric manifestations have been associated with a decreased

quality of life[5,8,19], increased functional disability[3], sleep disorders[21,22], increased unemployment rate[23,34] and health service utilization[25,26].

There is still little consensus on the role of laboratory tests and imaging techniques in the diagnosis of psychiatric syndromes and due to the lack of simple diagnosis process, psychiatric syndromes are frequently undiagnosed.

This manuscript pretends to a be systematic review on the recent literature focused in the study of screening tools for the identification of SLE patients with probable cognitive dysfunction, mood disorders or anxiety disorders, the three most prevalent psychiatric manifestations in lupus.

METHODS

A Pubmed/Medline and Scopus search was conducted from January 2002 to January 2012 using the following keywords: “neuropsychiatric lupus” or “systemic lupus erythematosus” combined with “diagnosis”, “anxiety disorders”, “mood disorders” and “cognitive dysfunction”. A follow-up of the relevant bibliography in articles was also done in order to identify additional relevant studies.

Abstracts of all identified studies were reviewed by two investigators. Every time an abstract was considered as potentially relevant, by either or both investigators, the full-text was retrieved and reviewed for relevance by applying the exclusion and inclusion criteria.

Review articles, case reports, studies in languages other than english or portuguese were immediately excluded. Included were all the articles investigating a screening tool for the diagnosis of psychiatric lupus. Studies that did not relate with diagnosis of psychiatric

manifestations in the lupus setting or with its laboratory and/or imaging diagnosis were also excluded.

RESULTS

The described search identified 446 articles (Figure I), of which 102 were considered as potentially relevant. Forty-seven articles were excluded based on abstract analysis. The remaining 55 studies were reviewed on its full text and the inclusion and exclusion criteria were applied. Thirteen studies were included in this systematic review.

COGNITIVE DYSFUNCTION

Difficulties in remembering, concentrating and performing cognitive-dependent activities are frequent complaints of SLE patients[27,28]. In fact Cognitive Dysfunction (CD) has been reported as one of the most frequent neuropsychiatric manifestations in SLE, having a prevalence in the adult population of 5,4 - 50 %[5,6,14,16,28-33] and in the pediatric population of 7,3 - 79,8 %[5,6,14,19,29,30].

In adults CD increases the risk of physical injury, reduces patients ability to properly adhere to treatment regimens and to function effectively in their home or work environments[17]. In pediatric patients cognitive impairment may prevent the normal development, with serious repercussions throughout life[34].

A comprehensive battery of neuropsychological tests is the ideal method to evaluate the presence and severity of cognitive dysfunction. However, in order to facilitate the diagnosis process, the ACR Ad Hoc Committee on NPSLE proposes an one-hour battery of brief mental status examinations (short ACR-SLE battery)[1].

The short ACR-SLE battery has been validated and found reliable in spite of high practice-effect observed in some tests by a study that tested the correlation between the short ACR-SLE battery and a comprehensive neuropsychological battery[35]. Nevertheless the short ACR-SLE battery is not easily available, requires administration by specialized professionals and is too expensive to be used in routine clinical consults[15,27,28].

The ANAM is a, 30 to 45 minutes self-administered, computerized battery of neuropsychological tests, developed by U.S. military in order to assess the cognitive repercussions of chemical agents, extreme environments and fatigue on cognitive processing speed and efficiency[27].

Holliday et al, in 2003, was the first to suggest the use of ANAM as a screening tool in the SLE context. This study administered both ANAM and a traditional test battery based on ACR Ad Hoc Committee on NPSLE recommendations in a sample of 67 ethnically mixed SLE patients enrolled in a large prospective cohort[27].

The results showed that many ANAM measures correlated with the scores from the traditional neuropsychological tests. It was also found that age is of little relevance on the variance observed when accounted alone but, it acts as a powerful moderator variable when is entered with ANAM variables into a linear regression model. This model accounted for about 61% of the variance in the average T-score on the traditional tests[27].

A Roebuck-Spencer, 2006 publication, confirms the positive correlation between ANAM and traditional neuropsychological testing. In this study the performances in the two batteries are compared in a sample of 60 SLE patients participating in a large SLE cohort on biomarkers of cognitive dysfunction. ANAM test battery demonstrated a sensibility of 76,2% and specificity of 82,8% on the classification of individuals with probable cognitive impairment versus no impairment in neuropsychological testing. ANAM remained a good

screening tool when depression and sleepiness were present, measured with validated self-reported measures of sleepiness and depressed mood, suggesting that it is not confounded by these. Furthermore, significant correlation between ANAM's mood scale and BDI-II was found, supporting its use as a potential measure of emotional distress in SLE patients[36].

A 2010 study by Hanly et al, sought out to compare ANAM battery tests' performance in a sample of 29 healthy controls, 68 Lupus (SLE), 33 Rheumatoid Arthritis (RA) and 20 Multiple Sclerosis (MS) patients[31].

The results showed a cognitive impairment of 11-50% in SLE patients (depending on stringency of classification rules) when compared with locally recruited healthy controls. However this frequency was comparable with the 9-61% calculated frequency in RA patients and lower than that calculated for MS patients, 20-75%. The frequency difference between SLE patients and patients with stable MS disease is expected but the observed comparability of frequencies between SLE patients and patients with a disease that does not affect primarily the CNS, as RA, raised questions about the presumed etiology of deficits detected by ANAM. The authors suggested that the measures evaluated by the ANAM battery do not distinguish between impaired mental processing and speed sensoriomotor deficiencies and can instead represent CNS immunosuppressive toxicity. Leading to the conclusion that ANAM can't be used to determine dysfunction on specific cognitive domains and it was not designed as a substitute for formal neuropsychological assessment[31].

In 2007 Brunner et al studied the statistical properties of the pediatric ANAM (ped-ANAM) in a childhood-onset SLE sample. Ped-ANAM and a battery of formal neuropsychological tests (based on published data for SLE adults) were performed in a

sample of 27 children with a median age of 16,5 years recruited from a pediatric rheumatology clinic. A trend towards worse performance of participants with CD compared to those without was observed in every performance parameter of the battery but statistically significant differences between the two groups were only reached for 3 out of the 10 ped-ANAM tests. Furthermore, statistical significant correlations were found between Ped-ANAM tests and formal neuropsychological tests. Ped-ANAM was found as a promising tool to screen cognitive dysfunction in SLE children presenting validity and promising sensitivity and specificity[15].

The Cognitive Symptom Inventory (CSI) is a self-administered paper questionnaire consisting of 21 items focused in evaluating the subject's ability to perform several cognitive functions and activities of daily life.

In 2002, Alarcón et al published a study which aimed determine the factor structure of the CSI and the production of 4 factor scales and their correlation with 3 self-report measures of cognitive dysfunction and self-report measures of fatigue, helplessness, self-efficacy, pain, social support and use of maladaptative coping skills. The sample, drawn from a large prospective cohort (LUMINA), consisted in 156 ethnically mixed SLE patients[17].

The four main factors assessed by the CSI were found to be: Attention/Concentration, Pattern/Activity Management, Intermediate Memory and Initiation of Executive Functions. Despite the small shared amount of common variance between these four factors, the correlation was not high enough that they duplicate one another[17].

Modest statistically significant correlations were also found between CSI cognitive factor scales and SLAM measure of Cortical Dysfunction, SF-36 measure of Mental Functioning,

SDI measure of Cognitive Impairment, measures of fatigue, psychological distress, social support, maladpative coping skills, self-efficacy and pain[17].

CSI patients' responses were found not to be confounded by social-demographic or clinical variables. The questionnaire was completed in an average time of 10 minutes and with minimal paraprofessional help regardless of ethnical backgrounds or administered language[17].

The Montereal Cognitive Assessment (MoCA) is a validated, one-page, physician-administred questionnaire used on the identification of mild cognitive dysfunction in the elderly[32].

Published in 2011 by Adhikari et al there is a study that aims to evaluate MoCA as a screening tool for detection of cognitive dysfunction in SLE patients. In a sample of 44 SLE patients recruited in the Cincinnati area (USA) were applied both the MoCA and, as gold standard, the ANAM[35]. Results demonstrate that to a standard cutoff score of 26 the sensitivity of MoCA was 83%. The specificity was 73% with a positive predictive valued of 50% and a negative predictive value of 92%. These results suggest that MoCA has the potential to be used as a screening tool for the detection of SLE with probable cognitive dysfunction[32].

In 2008, Kozora et al publishes a study aimed to examine the screening utility of the standardized neurologic evaluations in the identification of SLE patients with probable cognitive dysfunction. All the participants in the study were already enrolled in a large prospective cohort of cognitive functioning and neuroimaging. The participants were selected based on the examination of their clinical history and on physician interview in order to identify the ones with history of neuropsychiatric diseases or depression. The Scripps Neurologic Rating Scale (NRS) and the short ACR-SLE battery were administrated

to all the participants (SLE=67, Controls=29)[37]. The NRS is a 22 item neurologic exam developed for the clinical evaluation of patients with multiple sclerosis.

The prevalence of cognitive dysfunction in the sample was 20,9%. The non-NPSLE group had worse outcomes on NRS global score than the control group (p<0,001). However after analysis of the NRS parameters, the one responsible for the statistically significant difference was “mentation and mood”. Nevertheless two patients were excluded after the initial screening process during the administration of the neurologic examination by the neurologist suggesting that the NRS can assure that overt neurologic dysfunction is not present and assist in identifying non-NPSLE patients[37].

Julian et al publishes, in 2011, a study aimed at the evaluation of the utility of telephone screening and self-report assessments of cognitive complaints in detecting cognitive impairment in individuals with SLE and RA[28].

Two screening measures were evaluated: a 12-15 minutes telephone interview based on three neuropsychological tests (see article for details) and the Perceived Deficits Questionnaire (PDQ), a five-question, self-administered questionnaire. A validated neuropsychological battery based on the short ACR-SLE battery was used as “gold standard”.

The sample of 138 SLE patients and 84 RA patients was drawn from two large cohorts of SLE and RA patients, respectively. The cognitive dysfunction rates were 27% to the SLE group. The telephone screening had 77% sensitivity, 65% specificity, 94% negative predictive value, 43% positive predictive value and 67% of the patients were correctly classified in the SLE group. While the PDQ had 64% sensitivity, 65% specificity, 83% negative predictive value, 38% positive predictive value and 64% of the patients were correctly classified in the SLE group.

Contrary to telephone screening measure, the PDQ was not a significant predictor of cognitive impairment when adjusted for social-demographic data and depression[28].

MOOD AND ANXIETY DISORDERS

The reported prevalence of mood and anxiety disorders in recent studies ranges between 12,4-60%[5,14,28,38-41] and 6,4-46,5%[5,29,39,41], respectively.

The ACR Ad Hoc Committee on NPSLE recommends the use of standardized instruments like the Center for Epidemiological Studies - Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale (HADS) for the diagnosis of mood and anxiety disorders[1].

Several associations have been sought out by different studies in order to understand the pathophysiology of these disorders.

The association between short disease duration and anxiety disorders was described in a 2011 study by Hawro et al, raising the hypothesis that anxiety was a consequence of the inadequate information about the disease suggesting that at least part of the anxious disorders encountered in NPSLE have an adaptive background[33].

Kozora et al in 2007 compared the performances of depressed SLE patients (n=13), depressive non-SLE patients (n=10) and healthy controls (n=25) in the short ACR-SLE battery and a comprehensive neuropsychological battery. The results of this study not only confirmed the association between depression and cognitive dysfunction[42] but also validated the short ACR-SLE battery for the diagnosis of cognitive dysfunction in depressed SLE patients[43].

In a survey study published by Iverson et al in 2002, two screening depression measures were compared, Beck Depression Inventory-Second Edition (BDI-II) and the British Columbia Major Depression Inventory (BCMDI), both instruments constructed according

to the diagnostic criteria of DSM-IV for depression. The sample consisted of 103 self-reported lupus patients (no attempt was made to confirm the diagnosis) and 136 healthy controls. The self-reported SLE group had higher rates of depression and vegetative symptoms (fatigue, difficulty falling asleep, sadness, etc.) than the control group. The results point to a possible over-estimate diagnosis of depression in this study of 103 SLE patients, as measured by the BDI-II, a test that is considered valid and reliable screening of depression. Fifteen percent of the patients identified as depressed on the BDI-II scored in the normal range on the BCMDI, and 46% scored in the possibly depressed range. Therefore, it is possible that the BDI-II over-identified depression in this sample[22].

In a 2011 study by Julian et al, the Center for Epidemiological Studies - Depression Scale (CES-D) is compared with the Mini-International Neuropsychiatric Interview (MINI), a validated diagnostic method based on structured clinical interview, in a sample of 150 SLE patients drawn from a prospective cohort of 957 lupus patients. In this sample 26% of the patients were diagnosed with a mood disorder and 17% with major depressive disorder measured by the MINI. The results showed a 92% of corrected classified patients with major depressive disorder and a 87% sensibility and specificity in detection of any mood disorder with the CES-D[40].

Hyphantis et al, 2011, studies the psychometric characteristics of the greek version of the Patient Health Questionnaire-9 (PHQ-9) in a diverse rheumatologic sample of 558 patients (62 lupus patients). The PHQ-9 is a, 9 question, self-administered, simple, questionnaire used on the screening and severity assessment of depression. The results showed 25,4% prevalence of Major Depressive Disorder, measured by MINI, and a 81,2% and 86,8%, sensitivity and specificity, respectively, of the greek version PHQ-9[44].

PILOT SCREENING TOOL

Mosca et al published, in 2011, a study aimed to create a questionnaire, to be administered by physicians, that could be used as a screening tool for the identification of neuropsychiatric manifestations in SLE patients with no obvious CNS involvement, for further evaluation[45].

Starting from group of 112 questions drawn from 41 questionnaires aimed at assessing neuropsychiatric manifestations similar to those prevalent in NPSLE, a panel of experts and statistic analysis created a draft questionnaire with 62 items. This draft questionnaire was then tested in 139 SLE patients from 11 european centers and the results were compared with clinical diagnosis made by a specialist. After additional statistical analysis, the final questionnaire consisted of 27 items, 15 referring to the central nervous system symptoms and 12 to psychiatric ones.

For a cutoff value of 17 the questionnaire had a sensitivity and specificity of 93% and 25% respectively. It was found that the association of non-specific symptoms (e.g. subjective complain of cognitive dysfunction or headache) may determine a higher score than serious manifestations such as seizures alone. All the initial included items aimed at the assessment of peripheral nervous system symptoms were excluded based on the methodology used. Despite the intent to be administered by a physician the authors considered the questionnaire to be simple enough to be filled by the patient himself[45].

DISCUSSION

One of the most controversial topics in the study of the psychiatric manifestations is their etiology. In fact, despite the high prevalences reported its still not known if they are a direct consequence of the autoimmune disease or secondary to it. Several factors can

explain the secondary nature of these disorders like the stress of having a chronic disease, the lack of social support or the use of immunosuppresive therapy[39].

Psychiatric syndromes are rarely diagnosed early in their course due to their initially faint clinical manifestations and lack of accepted, valid and accessible methods of detection which leads to under-diagnosis and under-treatment of these conditions. Thus, a simple, sensitive screening test would serve to improve quality of management of lupus patients[32]. On the other hand, randomized clinical trials are necessary in SLE to fully understand the benefit-harm tradeoffs for screening these psychiatric manifestations[40].

Some instruments with the intend of screening cognitive dysfunction in SLE patients have been recently analyzed. However a lot more research needs to be done in order to validate them. With the exception of ANAM, all the instruments proposed as screening tests across the literature were studied only once.

The ANAM presents as the most analyzed of the screening tools, presenting good sensitivity and specificity (76,2% and 82,4%, respectively) on the distinction of SLE patients with cognitive dysfunction in formal neuropsychological testing from those without. ANAM presents as a instrument with less sensitivity to confounding variables such as, education, English proficiency and possible ethnic differences compared to the formal neuropsychological testing[27]. Its accessibility, self-administration, low practice-effects, reduced cost and validity in depressed lupus patients[27,36] makes of ANAM a promising screening. The finding that it may be confounded by immunosuppressive toxicity and/or sensoriomotor deficits[31] may not be as relevant clinically as it is etiologically since regardless of cause attribution, cognitive dysfunction is a co-morbidity that needs to be addressed when diagnosed.

Preliminary results determined that Cognitive Symptom Inventory (CSI), a 10 minutes self-administered paper test, has the potential to be used as a screening instrument on the identification of SLE patients with probable cognitive dysfunction. Revision of some of the items' content, expansion of the questionnaire so it covers other cognitive domains, study of its psychometric characteristics and testing it in different samples are some of the subjects that need to be addressed in further studies in order to validate the CSI as a screening tool[17]. Contrary to CSI, the Perceived Deficits Questionnaire, a 5 question self-administered questionnaire was found to be a weak predictor of cognitive impairment since it was confounded by social-demographic data and depression[28].

The Montereal Cognitive Assessment (MoCA), a physician administered questionnaire, presented a 83% sensitivity and 73% specificity. However the "gold standard" used was not formal neuropsychological testing but ANAM, which represents a vulnerability of the study[32].

In the Kozora et al study on the utility as a screening tool of the Scripps Neurologic Rating Scale[16] the results were not too impressive since despite the significant difference between SLE and control groups in identifying cognitive dysfunction, "mentation and mood" was the parameter responsible for the statistically significant difference. Furthermore, one aspect that was not referred in the study was how long did it take to administer the neurologic exam, essential to determine the true time-cost efficiency of it.

Another promising screening instrument is the Telephone Screening studied by Julian et al, the 43% positive predictive value and 93% negative predictive value presented by this tool, is an advantage in that permits to exclude with greater confidence individuals without cognitive impairment[28].

It is somehow surprising that despite the high frequencies reported of mood and anxiety disorders among lupus patients, and the number of measures available aiming the screening of these disturbances, only two studies were found comparing the performances of these tests in the lupus context. In fact, only in 2011 the Center for Epidemiological Studies Depression Scale (CES-D), recommended in 1999 by the ACR Ad Hoc Committee on NPSLE as a screening tool to identify patients with probable mood disorders, was tested, presenting a 87% sensitivity and specificity in detecting any mood disorder when compared with MINI[40].

Studies like the one published by Hyphantis et al, that validated the greek version of PHQ-9 in a large and diverse rheumatologic sample[44], are very important since questionnaires when translated need to be validated again in order to guarantee their quality.

Pediatric Neuropsychiatric Lupus (Ped-NPSLE) is even less understood than the adult form due to the lack of studies published. The definition cases and diagnostic criteria and testing recommended by the ACR Ad Hoc Committee on NPSLE are being inadequately used in children. Williams et al demonstrated that depending on the methodology used to classify cognitive impairment in children, the prevalence of cognitive dysfunction ranged from 7,3% to 63,4% in the same sample. More than that no significant differences were encountered in tested domain scores as well as cognitive dysfunction prevalence estimates between lupus children and controls[19]. Another difficulty in studying pediatric lupus is the small sample available, one of the main limitations of the Brunner et al study[15], that examined the usefulness of the pediatric version of ANAM in small sample of 27 lupus children.

Mosca et al approached screening testing in a holistic way, creating a physician-adminestered simple questionnaire to screen neuropsychiatric events. The main limitation of the study is the lack of items that assess the peripheral nervous system, justified by the authors as a result of the low prevalence of these phenomena in the lupus context. Despite the low specificity demonstrated (25%) this is a revolutionary study that demonstrated promising preliminary results[45].

There is still a long way to go regarding Neuropsychiatric Lupus. Sample selection, classification of impairment and attribution of cause are parameters that need to be defined and standardized in order to compare studies and draw conclusions.

The screening of psychiatric manifestations needs to be evaluated through randomized clinical trials in its true utility since the impact of early intervention on these phenomena is still unknown.

The translation and validation of screening tools in portuguese might facilitate and estimulate the study of neuropsychiatric lupus in Portugal.

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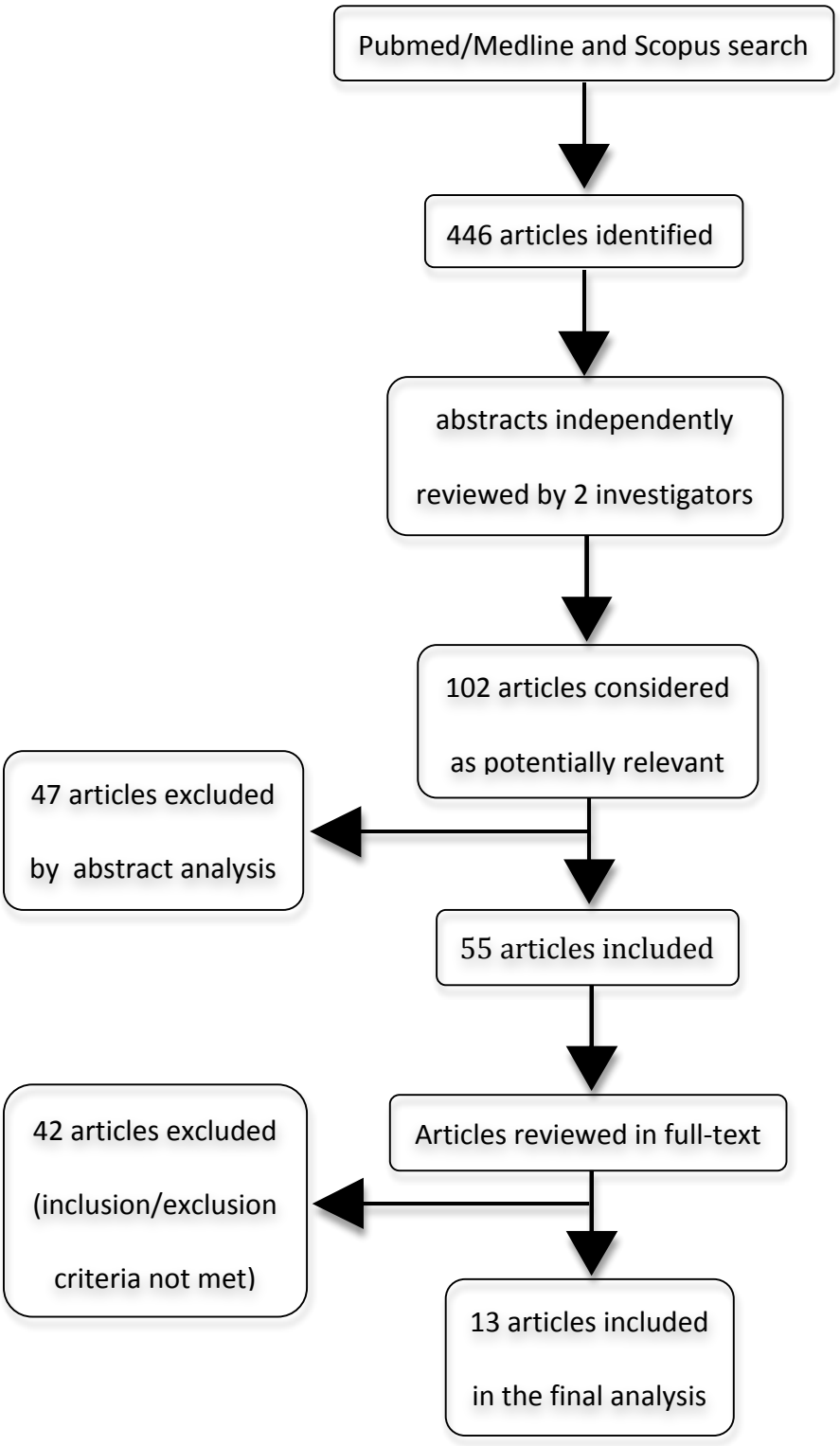

Figure I Flowchart showing research process

Normas de publicação
Revista Acta Reumatológica Portuguesa

A Acta Reumatológica Portuguesa publica artigos originais sobre todos os temas da Reumatologia ou com ela relacionados. São também publicados artigos de revisão, casos clínicos, imagens, cartas ao editor e outros que se incluam na estrutura editorial da revista (recomendações, artigos sobre prática clínica reumatológica, notícias de reuniões de sociedades científicas, por ex.).

A Acta Reumatológica Portuguesa subscreve os requisitos para apresentação de artigos a revistas biomédicas elaboradas pela Comissão Internacional de Editores de Revistas Médicas (*International Commitee of Medical Journal Editors*), publicada na íntegra inicialmente em N Engl J Med 1991; 324: 424-28 e actualizada em Outubro de 2008 e disponível em www.ICMJE.org. A potítica editorial da Acta Reumatológica Portuguesa segue as Recomendações de Política Editorial (*Editorial Policy Statements*) emitidas pelo Conselho de Editores Científicos (*Council of Science Editors*), disponíveis em www.councilscienceeditors.org/services/draft_approved.cfm.

A Revista está indexada no PubMed/Medline e os artigos estão disponíveis *online* na íntegra, com acesso aberto e gratuito.

Os artigos devem preferencialmente ser redigidos em inglês. Os artigos em língua portuguesa também podem ser submetidos para apreciação.

O rigor e a exactidão dos conteúdos, assim como as opiniões expressas são da exclusiva responsabilidade dos autores.

Os autores devem declarar potenciais conflitos de interesse.

Os artigos não podem ter sido anteriormente publicados noutra revista. Quando o artigo é aceite para publicação é mandatório o envio via e-mail de documento digitalizado, assinado por todos os autores, com a transferência dos direitos de autor para a Acta Reumatológica Portuguesa.

Os artigos publicados ficarão propriedade da revista, não podendo ser reproduzidos, no todo ou em parte, sem autorização dos editores.

A aceitação dos originais enviados para publicação é sempre condicionada a avaliação pelos consultores editoriais. Nesta avaliação os artigos poderão ser:

a) aceites sem alterações;

b) aceites após modificações propostas pelos revisores;

c) recusados.

Em todos os casos os pareceres dos consultores serão integralmente comunicados aos autores.

Quando são propostas alterações, o autor deverá enviar via e-mail no prazo de 1 mês, uma carta ao editor e a cada um dos revisores respondendo a todas as questões colocadas e uma versão revista do artigo com as alterações inseridas destacadas com cor diferente.

Instruções aos Autores

Todos os manuscritos que não estejam em conformidade com as instruções que se seguem podem ser enviados para modificações antes de serem revistos pelos consultores.

Todos os trabalhos devem ser enviados por e-mail para: **edtecnicarp@gmail.com.**

Os manuscritos devem ser acompanhados de declaração de originalidade e de cedência dos direitos de propriedade do artigo, assinada por todos os autores, conforme minuta publicada em anexo.

O texto deve ser enviado em formato digital (e-mail), a dois espaços, com letra tamanho12 e com margens não inferiores a 2,5 cm, em Word para Windows. Todas as páginas devem ser numeradas.

As imagens devem ser fornecidas independentemente do texto em formato JPEG ou TIFF.

Os textos devem ser organizados da seguinte forma:

Página 1

a) Título em português e inglês

b) Nome dos autores e respectiva afiliação

c) Serviço(s) ou organismo(s) onde o trabalho foi executado

d) Subsídio(s) ou bolsa(s) que contribuíram para a realização do trabalho

e) Morada e e-mail do autor responsável pela correspondência relativa ao manuscrito

f) Título breve para rodapé

Página 2

a) Título (sem autores)

b) Resumo em português e inglês, que para os artigos originais deve ser estruturado da seguinte forma: Objectivos, Material e Métodos, Resultados, Conclusões. O resumo dos artigos originais não deve exceder as 350 palavras e o dos casos clínicos as 180 palavras.

c) Palavras-chave em português e em inglês (Keywords)

Um máximo de 5 palavras-chave, utilizando a terminologia que consta na lista do Index Medicus: «Medical Subject Headings» (MeSH), deve seguir-se ao resumo.

Página 3 e seguintes

Artigos originais: O texto deve ser apresentado com os seguintes subtítulos: Introdução (incluindo Objectivos), Material e Métodos, Resultados, Discussão, Conclusões, Agradecimentos (se aplicável), Referências.

Os artigos originais não deverão exceder as 4.000 palavras, com um total de 6 figuras/tabelas e 60 referências.

Caso clínico: os subtítulos serão, Introdução, Caso clínico, Discussão, Referências.

O caso clínico não deve exceder as 2.000 palavras e 25 referências. Deve ser acompanhado de figuras ilustrativas. O número de tabelas/figuras não deve ser superior a 6.

A partir da segunda página, inclusive, todas as páginas devem ter em rodapé o título breve indicado na página 1.

Referências: As referências bibliográficas devem ser classificadas e numeradas por ordem de entrada no texto, em *superscript* e não entre parêntesis. As abreviaturas usadas na nomeação das revistas devem ser as utilizadas pelo *Index Medicus*.

Nas referências com 6 ou menos autores todos devem ser nomeados. Nas referências com 7 ou mais autores devem ser nomeados os 3 primeiros seguidos de et al.

Notas: Os números da página inicial e final devem ser totalmente apresentados (565-569 e não 565-9)

Não indicar o número da revista nem o mês da publicação.

Seguem-se alguns exemplos de como devem constar os vários tipos de referências:

– *Revista*

Apelido e iniciais do(s) autor(es). Título do artigo. Nome da revista Ano; Volume: Páginas.

Ex.: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic. Ann Rheum Dis 1992; 51:195-197.

– *Artigo publicado online (inserir DOI)*

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008. 097758

– *Capítulo de livro*

Nome(s) e iniciais do(s) autor(es) do capítulo. Título do capítulo. In: Nome(s) e iniciais do(s) editor(es) médico(s). Título do livro. Cidade: Nome da casa editora, ano de publicação: primeira a última página do capítulo.

Ex.: Stewart AF. Hypercalcemia resulting from medications. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorder of Mineral Metabolism. New York: Raven Press, 1993: 177-178.

– *Livro*

Nome(s) e iniciais do(s) autor(es). Título do livro. Cidade: Nome da casa editora, ano de publicação: página(s).

Ex.: Lorig K. Patient Education. A practical approach. St. Louis: Mosby-Year Book;1992: 51.

– *Documento electrónico*

Ex: Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde - Divisão de Doenças Transmissíveis, Março de 2005 http://www.dgsaude.pt/upload/membro.id/ ficheiros/ i006875.pdf. Acedido em 25 Janeiro de 2008

As referências a trabalhos ainda não publicados, comunicações em reuniões, não publicadas em livros de resumos, ou comunicações pessoais devem ser citadas no texto e não como referências formais.

A exactidão e o rigor das referências são da responsabilidade do autor.

Tabelas: As tabelas a inserir devem ser assinaladas no texto em numeração romana e cumprir o limite descrito acima. Cada tabela deverá ser apresentada em folha separada, dactilografada a 2 espaços. Na parte superior devem apresentar um título sucinto mas informativo, de modo a poder ser compreendido sem recurso ao texto. Na parte inferior da tabela deve constar a explicação das abreviaturas utilizadas. Nas tabelas devem ser evitados os traços verticais e os traços horizontais, estes devem servir apenas como separadores de títulos e subtítulos.

Figuras: As figuras a inserir devem ser assinaladas no texto em numeração árabe e cumprir o limite definido acima. As legendas das figuras devem ser dactilografadas a dois espaços numa folha separada, depois da bibliografia. As figuras devem ser enviadas em suporte informático com ficheiros separados para cada figura, em formato JPEG ou TIFF.

Editoriais: Os editoriais serão solicitados por convite do Editor. Os editoriais serão comentários sobre tópicos actuais ou sobre artigos publicados na revista. O texto dos editoriais não deve exceder as 1.200 palavras, um máximo de 15 referências e não deve conter quadros ou figuras.

Artigos de revisão: Estes artigos serão preferencialmente solicitados pelo Editor. No entanto, os autores interessados em apresentar um artigo de revisão podem contactar o Editor para discussão dos tópicos a apresentar.

O artigo de revisão não deve exceder as 4.000 palavras, 6 tabelas/figuras e 100 referências.

Cartas ao Editor: As cartas ao editor devem constituir um comentário crítico a um artigo da revista ou uma pequena nota sobre um tema ou caso clínico. Não devem exceder as 600 palavras, uma figura ou um quadro, e um máximo de 10 referências bibliográficas.

Imagens em reumatologia: Podem ser submetidas imagens de particular interesse. As figuras, no máximo de 4, devem ser enviadas em formato JPEG ou TIFF de boa resolução. O texto acompanhante não deve ultrapassar as 500 palavras.

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As provas tipográficas serão, sempre que possível, enviadas aos autores contendo a indicação do prazo para revisão consoante as necessidades editoriais da revista.

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